REMARKS

Claim Amendments

Support for the claim amendments is found throughout the specification including, for example, at page 27, lines 8 to page 33, line 7.

Item 2: Rejection of Claim 5 Under 35 U.S.C. § 102(b) As Being Anticipated by Konno *et al.*

Claim 5 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Konno *et al.* (*Int. Arch. Allergy Immunol.*, 105:308-316 (1994)) for the reasons set forth in Paper No. 5. In Paper No. 5, the Examiner had alleged that the cited reference teaches "a method of treating an individual mouse . . . by the administration of a therapeutically effective amount of an anti-TNF-α antibody (see Table 3, in particular)." The Examiner also urges that "by decreasing air overflow in rats made airway hyperresponsive by the administration of LPS, the prior art teaches treatment of airway inflammation." Paper No. 5, at page 3.

Applicant respectfully disagrees with the Examiner's conclusion that Claim 5 is anticipated by the Konno *et al.* reference. The Court of Appeals for the Federal Circuit has stated that "[u]nder 35 U.S.C. § 102, anticipation requires that each and every element of the claimed invention be disclosed in a prior art reference." Akzo N.V. v. International Trade Comm., 11 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986) (citations omitted).

Claim 5, as amended, relates to a method of treating airway inflammation associated with asthma in a human comprising administering an anti-TNFα antibody or antigen-binding fragment thereof to the human.

In contrast, Konno *et al.* describe experiments that were designed to examine the influence of roxithromycin (RXM), a macrolide antibiotic, on cytokine appearance in mouse lung extract induced by lipopolysaccharide (LPS) inhalation and on bronchial responsiveness (BR) to methacholine (Mch) in LPS-treated mice.

The endotoxin (LPS)-mouse system used by Konno *et al.* is not an animal model for asthma because it is known that: (1) inhalation of endotoxin causes an increase in BR in ***both*** normal and asthmatic subjects and (2) local administration of endotoxin to airways in experimental animals causes pulmonary inflammatory responses with an increase in BR (Konno *et al.*, page 315, column 1, paragraph lines 6-11). The endotoxin-mouse system is an animal model that features acute lung inflammation during infection.

Konno *et al.* found that intratracheal injection of LPS resulted in the appearance of inflammatory cytokines in airways and lungs which was inhibited by pre-treatment with RXM (Konno *et al.*, page 315, column 1, paragraph 2, lines 13-17; and Table 1). Konno *et al.* found that the increase in BR to Mch observed in LPS-injected mice was also diminished by pre-treatment with RXM (Konno *et al.*, page 315, column 1, paragraph, lines 17-19; and Table 2). The authors concluded that "[t]hese results strongly suggests that RXM orally administered into mice inhibits inflammatory cytokine production in airways and results in a therapeutic effect on LPS-induced increase in BR to Mch" (Konno *et al.*, page 315, column 1, paragraph 2, lines 19-22).

Konno *et al.* also found that pre-treatment with RXM partially blocked the appearance of TNF in aqueous lung extracts, as well as an increase in BR to Mch (Konno *et al.*, page 315, sentence bridging columns 1 and 2; and Tables 1 and 2). Konno *et al.* further found that pre-treatment of mice with an anti-TNF antibody prior to the appearance of inflammatory cytokines in airways and lungs inhibited the LPS-induced increase in methacholine (Mch) responsiveness (Konno *et al.*, page 315, column 1, lines 2-3; and Table 3). The authors concluded that these results indicate "that the protective effect of RXM on BR may be due to its suppressive effect on TNF-α release and that TNF-α mediates at least partly the increase in responsiveness occurring after LPS administration" (Konno *et al.*, page 315, column 2, lines 4-7).

Thus, the method of Claim 5 differs from the method taught by Konno *et al.* in the subject treated (a human versus a mouse). Accordingly, Claim 5 is not anticipated by the Konno *et al.* reference. Reconsideration and withdrawal of the rejection of Claim 5 under 35 U.S.C. § 102(b) are respectfully requested.

Items 3 and 4: Rejections Under U.S.C. § 103

Claim 1 stands rejected under 35 U.S.C. § 103 as being unpatentable over Konno *et al.* in view of Shah *et al.* (*Clin. Exper. Allergy*, 25:1038-1044 (1995)) for the reasons set forth in Paper No. 5. In Paper No. 5, the Examiner had urged that one of ordinary skill in the art would have been motivated to treat asthma with the anti-TNFα taught by Konno *et al.* "because the anti-TNF-α antibody taught by Konno et al., was effective in reducing airway hyperresponsiveness in LPS treated mice and airway hyperresponsiveness is a characteristic feature of bronchial asthma, as taught by Konno et al." Paper No. 5, at page 4, lines 13-17. The Examiner had also urged that one of ordinary skill in the art would have been motivated to treat asthma with the anti-TNFα taught by Konno *et al.* "because Shah *et al.*, teaches TNF-α is an important mediator of asthma

and that patients with symptomatic asthma had 20 times greater amounts of TNF-α in their lung fluid then asymptomatic patients and that an anti-TNF-α monoclonal antibody had exciting and dramatic beneficial results in treating rheumatoid arthritis and that since TNF-α plays a fundamental role in both the inflammation and acquired bronchial hyperresponsiveness it raises possible new therapeutic intervention in the treatment of asthma." Paper No. 5, at page 4, lines 17-24.

Claims 2 and 6 also stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Konno *et al.* in view of Shah *et al.* and further in view of U.S. Patent No. 5,698,195 (hereinafter "the Le '195 patent"). In Paper No. 5, the Examiner had urged that one of ordinary skill in the art would have been motivated to make a chimeric antibody as taught by the Le '195 patent "because the use chimeric antibodies over antibodies derived from a single non-human species [to] reduce the immunogenicity of the antibody in application and allow for increased yields" (Paper No. 5, at page 4, last paragraph).

Applicant respectfully disagrees that Claims 1, 2 and 6 are obvious in view of the cited references. A *prima facie* case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable expectation of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not Applicants' disclosure. Id.

Teachings of the Cited References

Konno *et al.*

As discussed above, Konno *et al.* describe experiments that were designed to examine the influence of roxithromycin (RXM), a macrolide antibiotic, on cytokine appearance in mouse lung extract induced by lipopolysaccharide (LPS) inhalation and on bronchial responsiveness (BR) to methacholine (Mch) in LPS-treated mice. At page 315, Konno *et al.* note that they used an endotoxin (LPS)-mouse system in these experiments because (1) "inhalation of endotoxin has been reported to cause an increase in BR" in ***both*** normal and asthmatic subjects and (2) "local administration of endotoxin to airways in experimental animals causes pulmonary inflammatory responses with an increase in BR" (Konno *et al.*, page 315, column 1, paragraph lines 6-11). It is important to note that endotoxin (LPS) inhalation has been reported to cause an increase in BR in ***both*** normal and asthmatic subjects. Thus, one of ordinary skill in the art would not view the

endotoxin (LPS)-mouse system as an animal model for asthma, but would rather consider it to be an animal model featuring acute lung inflammation during infection.

Konno *et al.* found that intratracheal injection of LPS resulted in the appearance of inflammatory cytokines in airways and lungs which was inhibited by pre-treatment with RXM (Konno *et al.*, page 315, column 1, paragraph 2, lines 13-17; and Table 1). Konno *et al.* found that the increase in BR to Mch observed in LPS-injected mice was also diminished by pre-treatment with RXM (Konno *et al.*, page 315, column 1, paragraph, lines 17-19; and Table 2). The authors concluded that "[t]hese results strongly suggests that RXM orally administered into mice inhibits inflammatory cytokine production in airways and results in a therapeutic effect on LPS-induced increase in BR to Mch" (Konno *et al.*, page 315, column 1, paragraph 2, lines 19-22).

Konno *et al.* also found that pre-treatment with RXM partially blocked the appearance of TNF in aqueous lung extracts, as well as an increase in BR to Mch (Konno *et al.*, page 315, sentence bridging columns 1 and 2; and Tables 1 and 2). Konno *et al.* further found that pre-treatment of mice with an anti-TNF antibody prior to the appearance of inflammatory cytokines in airways and lungs inhibited the LPS-induced increase in methacholine (Mch) responsiveness (Konno *et al.*, page 315, column 1, lines 2-3; and Table 3). The authors concluded that these results indicate "that the protective effect of RXM on BR may be due to its suppressive effect on TNF-α release and that TNF-α mediates at least partly the increase in responsiveness occurring after LPS administration" (Konno *et al.*, page 315, column 2, lines 4-7).

As stated above, the endotoxin (LPS)-mouse system used by Konno *et al.* is not an animal model for asthma because it is known that: (1) inhalation of endotoxin causes an increase in BR in ***both*** normal and asthmatic subjects and (2) local administration of endotoxin to airways in experimental animals causes pulmonary inflammatory responses with an increase in BR (Konno *et al.*, page 315, column 1, paragraph lines 6-11). The endotoxin-mouse system is an animal model that features acute lung inflammation during infection. Thus, Konno *et al.* do not teach or suggest that an anti-TNFα antibody can be used to treat asthma.

Shah *et al.*

The Shah *et al.* reference is a review article summarizing the scientific rationale in 1995 that supported TNFα as an attractive target for asthma. However, although Shah *et al.* report information from both *in vitro* and *in vivo* human and mouse studies, no data were disclosed showing that blocking TNFα would treat asthma.

Moreover, contrary to the Examiner's assertion, Shah *et al.* would not have motivated one of ordinary skill in the art to treat asthma in a human patient with the anti-TNFα taught by Konno *et al.* At best, Shah *et al.* invite one of ordinary skill in the art to explore "the possibility of a new type of therapeutic intervention" in the treatment of asthma. However, an invitation to conduct future experiments to identify a possible method of therapy of asthma is insufficient to provide a teaching or suggestion of the method of therapy with any reasonable expectation of success.

Evidence that the Shah *et al.* reference would not have motivated one of ordinary skill in the art to treat asthma in a human patient with the anti-TNFα is provided in the cited reference.

First, it is noted that the Shah *et al.* reference is entitled "Tumour necrosis factor alpha: a ***potential*** mediator of asthma" (emphasis added).

Second, at page 1039, column 2, Shah *et al.* report that "Considerable evidence has accumulated ***suggesting*** that TNFα upregulation occurs in asthmatic subjects, especially those with acute severe symptoms" (Shah *et al.*, column 2, lines 12-14; emphasis added). The "considerable evidence" reported by Shah *et al.* included: (1) increased levels of TNFα in sputum of patients with acute attacks of asthma; (2) increased number of cells expressing TNFα mRNA in bronchoalveolar lavage (BAL) fluid of stable atopic asthmatic subjects when compared to BAL of normal subjects; and (3) TNFα levels up to 20 times greater in BAL fluid of patients with symptomatic asthma than asymptomatic patients (see Shah *et al.*, page 1039, column 2, lines 14-33). At page 1040, column 2, Shah *et al.* conclude that "it ***appears*** that there is a disease related upregulation of TNFα ***which suggests that this cytokine plays a key role in ongoing airways inflammation***" (Shah *et al.*, page 1040, column 2, lines 6-8; emphasis added).

Third, at page 1040, column 2, Shah *et al.* report that "recent research indicates that ***TNFα maybe associated with acquired airway hyperresponsiveness***, a pathophysiological hallmark of asthma" (Shah *et al.*, column 2, lines 10-12; emphasis added). Shah *et al.* postulate that "TNFα can cause airway hyperresponsiveness either directly by affecting the bronchial smooth muscle or indirectly through release of inflammatory mediators or through a combination of mechanisms" (Shah *et al.*, page 1040, column 2, lines 40-44).

Fourth, at page 1041, column 1, and page 1042, column 2, Shah *et al.* report that TNFα augments inflammatory cellular influx into the bronchial mucosa by upregulating the expression of adhesion molecules on the microvasculature and the subsequent recruitment and activation of inflammatory cells.

Fifth, at page 1042, column 1, Shah *et al.* report that "exciting and dramatic beneficial results" have been obtained in the treatment of rheumatoid arthritis with an anti-TNFα antibody (Shah *et al.*, column 1, lines 16-21). However, one of ordinary skill in the art would not reasonably have expected that results obtained in treating rheumatoid arthritis with an anti-TNFα antibody would translate into clinical benefit with used in treating asthma, a condition that is unrelated to rheumatoid arthritis.

In fact, Shah *et al.* conclude their article by stating that "***it would be presumptuous*** to describe TNFα as 'the' mediator of asthma" (Shah *et al.*, page 1042, column 2, lines 21-23; emphasis added), but "its emerging fundamental role in both inflammation and acquired bronchial hyperresponsiveness" "***raises the possibility*** of a new type of therapeutic intervention" in the treatment of asthma (Shah *et al.*, page 1042, column 1, last two sentences; emphasis added).

Thus, while Shah *et al.* express hope that an anti-TNFα antibody would provide a new type of therapeutic intervention in the treatment of asthma, the cited reference does not teach or suggest that clinical benefit would in fact occur. The cited reference does not provide evidence or data that would have led one of ordinary skill in the art to expect that an anti-TNFα antibody could be used to treat asthma.

Le '195 Patent

In Paper No. 5, the Le '195 patent had been cited by the Examiner as teaching "how to make chimeric antibodies" and for teaching "the use of chimeric antibodies over antibodies derived from a single non-human species because they reduce the immunogenecity of the antibody in application and allow for increased yields" (Paper No. 5, at page 4, second paragraph from bottom).

Combination of References

As discussed above, Konno *et al.* disclose results from experiments conducted using an animal model that features acute lung inflammation during infection, but is not an animal model for asthma. Shah *et al.* invite one of ordinary skill in the art to explore the possibility of an anti-TNFα antibody as a new type of therapeutic intervention in the treatment of asthma. As such, the cited combination of Konno *et al.* and Shah *et al.* would not have suggested Applicant's claimed method of treating asthma to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success. The cited combination of Konno *et al.*, Shah *et al.* and the Le '195 patent would not have suggested Applicant's claimed method of treating airway inflammation associated with asthma to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success. Thus, the claimed invention is not *prima facie* obvious in view of the cited combinations of references.

Reconsideration and withdrawal of the rejections of Claim 1, 2 and 6 under 35 U.S.C. § 103 are respectfully requested.

Item 5: Rejections of Claims 1-12 Under 35 U.S.C. § 103

Claims 1-12 stand rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 5,698,195 (Le '195 patent) in view of Shah *et al.* and Lukacs *et al.* (*J. Immunol.*, 154:5411-5417 (1995)). Applicant respectfully disagrees that Claims 1-12 are obvious in view of the cited references.

Teachings of the Cited References

Le '195 Patent

In Paper No. 5, the Le '195 patent had been cited by the Examiner as teaching "a chimeric antibody cA2, which has high affinity, epitope specificity and the ability to neutralize the cytotoxic effects of human TNF-α" (Paper no. 5, at page 5, lines 5-7). In Paper No. 5, the Le '195 patent had also been cited by the Examiner as teaching "the use of a therapeutically effective amount of the cA2 antibody in treating a subject (i.e. an individual) having a pathology associated with abnormal levels of TNF-α, when compared with the levels of TNF-α in a normal healthy subject" (Paper no. 5, at page 5, lines 7-10).

Shah *et al.*

The Shah *et al.* reference is discussed in detail above. In summary, the Shah *et al.* reference is a review article summarizing the scientific rationale in 1995 that supported TNFα as an attractive target for asthma. However, although Shah *et al.* report information from both *in vitro* and *in vivo* human and mouse studies, no data were disclosed showing that blocking TNFα would treat asthma. Thus, while Shah *et al.* express hope that an anti-TNFα antibody would provide a new type of therapeutic intervention in the treatment of asthma, the cited reference does not teach or suggest that clinical benefit would in fact occur.

At best, Shah *et al.* invite one of ordinary skill in the art to explore "the possibility of a new type of therapeutic intervention" in the treatment of asthma. In particular, Shah *et al.* invite one of ordinary skill in the art to explore the possibility of an anti-TNFα antibody as a new type of therapeutic intervention in the treatment of asthma.

Lukacs *et al.*

Lukacs *et al.* describe a study designed to examine the role of TNF in the initiation and maintenance of leukocyte recruitment in airway inflammation induced by intratracheal challenge with soluble parasite (*Schistosoma mansoni*) egg Ag (SEA). The SEA-induced airway inflammation model used by Lukacs *et al.* is a model of Th2 cell-induced eosinophilic airway inflammation that allows for the study of the recruitment of various leukocyte subsets to lungs and airways (Lukacs *et al.*, page 5412, column 1, lines 12-16). This model of airway inflammation is characterized as having both an early neutrophilic (8-h) and a later (48-h) eosinophilic airway infiltration (Lukacs *et al.*, page 5415, column 2, last paragraph).

Lukacs *et al.* found that TNF mRNA expression and protein production were observed early during SEA-induced airway inflammation, and subsequently decreased to levels observed in vehicle-control-treated animals (Lukacs *et al.*, page 5415, column 2, last paragraph). Lukacs *et al.* also found that intratracheal SEA-challenged mice treated with the TNF receptor sTNFr-:Fc demonstrated significantly decreased recruitment of neutrophils and eosinophils into the lung and airway. The authors concluded that the results indicate that TNF-α mediates the recruitment of neutrophils and eosinophils during SEA-induced airway inflammation.

However, Lukacs *et al.* treated mice with a TNF receptor, not with an anti-TNF antibody. One of ordinary skill in the art would not reasonably have predicted given the results obtained by Lukacs *et al.* using a TNF receptor that an anti-TNF antibody could be used, with a reasonable expectation of success, in methods of treating asthma, in methods of treating airway

inflammation associated with asthma, and in methods of reducing accumulation in lungs of inflammatory cells associated with asthma.

Recent papers have been published reporting that TNF-α plays a central role in asthma and airway inflammation, while other recent papers have been published reporting that TNF does not have a critical proinflammatory role in asthma or airway inflammation. For example, Rudmann *et al.* (*Am. J. Physiol. Lung Cell Mol. Physiol.*, 279:L1047-L1057 (2000) (attached hereto as Exhibit 1)) demonstrated that blockade of TNF bioactivity did not abrogate allergic inflammation in mice deficient in TNF receptors and in wildtype mice treated with anti-TNF neutralizing antibody. However, Matheson *et al.* (*Am. J. Respir. Cell Mol. Biol.*, 27:396-405 (2002); attached hereto as Exhibit 2)) report that the role of TNF-α in toluene diisocynate (TDI)-induced asthma was demonstrated in TNF-α-deficient mice, produced by either administration of neutralizing antibodies or by deletion of the gene controlling TNF receptors, with the abatement of TDI-induced airway hyperresponsiveness and inflammation, but not specific antibody formation. These recent papers provide evidence that one of ordinary skill in the art would not have been able to predict given the teachings of Lukacs *et al.* whether administration of an anti-TNF antibody to a subject would be effective in methods of treating asthma, in methods of treating airway inflammation associated with asthma, and in methods of reducing accumulation in lungs of inflammatory cells associated with asthma.

Combination of References

As discussed above, the Le '195 patent teaches the use of a therapeutically effective amount of the cA2 antibody in treating a subject having a pathology associated with abnormal levels of TNF-α, when compared with the levels of TNF-α in a normal healthy subject. Shah *et al.* invite one of ordinary skill in the art to explore the possibility of an anti-TNFα antibody as a new type of therapeutic intervention in the treatment of asthma. Lukacs *et al.* teach the administration a TNF receptor to SEA-challenged mice, but not the administration of an anti-TNF antibody. Rudmann *et al.* and Matheson *et al.* provide evidence that one of ordinary skill in the art would not have been able to reasonably predict with an expectation of success, given the teachings of Lukacs *et al.*, whether administration of an anti-TNF antibody to a subject would be effective in methods of treating asthma, in methods of treating airway inflammation associated with asthma, and in methods of reducing accumulation in lungs of inflammatory cells associated with asthma. As such, the cited combination of the Le '195 patent, Shah *et al.* reference and

Lukacs *et al.* references would not have suggested to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success, Applicant's claimed method of treating asthma, Applicant's claimed method of treating airway inflammation associated with asthma or Applicant's claimed method of reducing accumulation in lungs of inflammatory cells associated with asthma. Thus, the claimed invention is not *prima facie* obvious in view of the cited combinations of references.

Reconsideration and withdrawal of the rejection of Claim 1-12 under 35 U.S.C. § 103 are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By _____

Helen Lee
Registration No. 39,270
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: November 18, 2004